REMARKS

Claims 1-8, 17,18, and 45 are presently pending. The amendments to claims 1, 3, 5, and 17 as well as new claim 45 are supported by the specification and do not contain new matter. Specifically, the amendments to claims 1 and 3 find support on page 5 of the specification, which states that "only a small subset of cellular plasminogen receptors, those that possess a carboxy-terminal lysine residue, participate in **cell surface** plasminogen activation" and that "[c]andidate plasminogen receptors possessing carboxy-terminal lysines include **p11**." The amendments to claims 1 and 3 also find support on page 25 of the specification, which states that the compositions of the invention are "usually employed in the form of pharmaceutical preparations" and recites a number of pharmaceutically acceptable carriers.

New claim 45 finds support in examples 8 and 9, on pages 43-45, and in figures 14-16. Example 8, which includes both *in vitro* and *in vivo* data, and accompanying figures 14 and 15 demonstrate that loss of p11 from the cell surface in a p11 antisense cell line (AS5 cell line) decreases matrix proteolysis, the invasiveness of the cells, and the metastatic potential of the cell line, i.e., the ability of HT1080 cells to extravasate and form tumors in the mouse lung. Furthermore, example 9 and accompanying figure 16 demonstrate a reduction in the number of metastatic foci and the size of tumors formed in subjects that received cancer cells treated with a composition that reduces p11 activity (AS5 cell line).

I. 35 U.S.C., Second Paragraph Rejections

In view of the amendments to claims 1, 3, 5 and 17, reconsideration is requested of the rejection of claims 1-8, 17 and 18 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Office asserts that claims 1-8, 17 and 18 are indefinite because a proper composition claim must have at least two different elements, while the present claims are said not to contain any recited elements or contain only one recited element. Claim 1 has been amended to recite two different elements: an antisense p11 polynucleotide

and a pharmaceutically acceptable carrier. Claims 2-8, 17 and 18 depend from claim 1. Also, claim 17 has been amended to remove the terms of multiple dependence. Given these amendments to the claims, the indefiniteness basis for rejection of the claims has been rendered moot.

II. 35 U.S.C., First Paragraph Rejections

In view of the amendments to claims 1, 3, and 17, reconsideration is requested of the rejection of claims 1-4, 17 and 18 under 35 U.S.C. §112, first paragraph. These claims were rejected on the basis that they do not satisfy the written description requirement.

Claim 1, as amended, is directed to a composition which modulates the activity of an extracellular p11 protein and affects a change in the level of plasminogen activation by a cell, the composition **comprising an antisense p11 polynucleotide** and a pharmaceutically acceptable carrier. The Office has asserted that claim 1 encompasses **any composition** that modulates activity of any p11 protein from any species and that the specification does not describe the structure of **any non-nucleic acid modulator** of a p11 protein.

Based on the applicant's election of Group I claims (claims 2-8, 17, and 18) in response to the restriction requirement of June 24, 2005, amended claim 1 is directed to a composition which comprises an **antisense p11 polynucleotide**. According to the Office, "the specification provides **adequate description** of the **antisense . . . nucleic acid modulators** targeted to the p11 described in the working examples." The applicant appreciates this well-reasoned finding and further asserts that the specification provides a representative number of species of p11 protein and antisense p11 polynucleotides in order to support the claimed genus. Specifically, the specification states that "the known primary structures of p11 are well conserved among vertebrates (e.g., chicken p11 is 89% identical and 97% similar to human p11) . . . such that the skilled artisan would reasonably expect p11 to have similar biochemical

properties among vertebrates."[1] Moreover, according to the specification, the utility of the composition of claim 1, namely reduced cellular invasion, *in any vertebrate* can be demonstrated without undue experimentation using a cultured cancer cell specific to the vertebrate and a simple cellular invasion assay[2]. The composition of claim 1, specifically the p11 antisense polynucleotide element, is also defined in the specification.

The specification defines a p11 antisense polynucleotide as a single stranded RNA or DNA molecule which is complementary to a p11 RNA that can be translated to produce a p11 polypeptide or a fragment thereof. In terms of function, the p11 antisense polynucleotide is described as being capable of decreasing the expression of p11 protein in a cell. The specification also discloses several species of p11 antisense polynucleotides that can be used in the invention, including a DNA or RNA as set forth in SEQ ID NO:5, SEQ ID NO:13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, or any of SEQ ID NO: 145-160[3].

In view of this comprehensive disclosure, one skilled in the art would discern that the applicant was in possession of the composition detailed in amended claim 1. Moreover, claims 2-4, 17, and 18, which depend from claim 1, contain all of the limitations of claim 1 and, therefore, satisfy the written description requirement for all of the reasons detailed with respect to claim 1. In addition to the reasons for satisfying the written description requirement detailed for claim 1, claims 2-4 and 7-11 more precisely define the invention such that a skilled artisan would recognize the applicant was in possession of the recited composition. In particular, amended claim 3 further defines *affecting* a change in the level of extracellular plasminogen activation, and amended claim 17 further defines the cell.

In light of the foregoing, applicant respectfully requests a withdrawal of the written description rejection of claims 1-4, 17, and 18.

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[1]Specification, page 23-24.
[2]Specification, page 24.
[3]Specification, page 17.

III. Rejection of claims 1-4, 17 and 18 under 35 U.S.C. §102(b) or §103(c)

Reconsideration is requested of the rejection of claims 1-4, 17 and 18 under §102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Yao et al.[4]

(a) 35 U.S.C. §102(b) rejection

Amended claim 1 is directed to a composition that modulates the activity of an **extracellular** p11 protein and affects a change in the level of **plasminogen activation** by a cell. The composition comprises an isolated p11 antisense polynucleotide and a pharmaceutically acceptable carrier.

The Yao et al. article discloses a plasmid that expresses p11 antisense mRNA and the transfection of a HeLa cell with the plasmid to study whether p11 inhibits the activity of the **intracellular** enzyme cytosolic phospholipase A_2 ($cPLA_2$)[5]. Nowhere does the Yao et al. reference disclose or suggest a composition comprising an isolated antisense polynucleotide and a pharmaceutically acceptable carrier that can modulate the activity of an extracellular p11 protein, as required by claim 1. The Yao et al. reference, in contrast, discloses the transfection of a cell with a vector having a p11 antisense mRNA, such that the amount of "**cellular p11 protein**" is reduced[6]. Moreover, nowhere does Yao et al. disclose or suggest that their p11 antisense mRNA modulates plasminogen activation, as required by claim 1.

A claim is anticipated only if each and **every element** as set forth in the claim is described in a single prior art reference.[7] Because Yao et al. do not disclose every element of claim 1, the reference does not anticipate claim 1. Claims 2-4, 17 and 18 incorporate all of the elements of claim 1 and are therefore, patentable in view of Yao et al. for all of the reasons detailed with respect to claim 1.

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[4]Dexamethasone Alters Arachidonate Release from Human Epithelial Cells by Induction of p11 Protein Synthesis and Inhibition of Phospholipase A_2 Activity, Yao et al., *The Journal of Biol. Chem.*, June 1999, 274(24): 17202-17208.
[5]Yao et al., pages 17202-3, 17205.
[6]Yao et al., page 17202.

The Office asserts that the compositions of the invention "change the level of plasminogen activation **in a cell**." This is not correct. As detailed in the specification, plasminogen is primarily synthesized in the liver and released into the circulation. It does not enter the cell. As such, and consistent with claim 1 of the invention, activity of an extracellular p11 protein is modulated by the claimed composition, which in turn, affects a change in the level of plasminogen activation. This all occurs extracellularly. As detailed above, nowhere does the cited art disclose a change in plasminogen activation. Rather, the cited art's focus is on an entirely different pathway involving arachidonic acid, which is a mediator in the inflammatory response, and all modulation of p11 activity takes place **intracellularly**.

The Office, however, asserts that since the antisense p11 polynucleotide of the Yao et al. reference meets **all the structural** limitations of claim 1, these polynucleotides would be considered to inherently change the level of plasminogen activation, as required by claim 1. This assertion is also not correct. Yao et al. doesn't disclose all of the structural limitations of the claim 1 composition. Claim 1 specifically requires a composition comprising an **isolated** p11 polynucleotide and **a pharmaceutically acceptable carrier**. Nowhere does the cited art disclose that their p11 polynucleotide is either isolated or a part of a composition with a pharmaceutically acceptable carrier. Moreover, the Patent Office has not met its required burden of proof regarding an inherency rejection of claim 1.

To properly support a determination of inherency, as a matter of Patent Office practice, it is incumbent on the Examiner to first provide rationale or evidence tending to show inherency.[8] In establishing this rationale or evidence, the Examiner must provide a basis in fact and/or technical reasoning to support the determination that the allegedly inherent characteristic necessarily flows from the teaching of the cited art.[9] Furthermore, "'[t]he mere fact that a certain thing **may result** from a given set of circumstances is not sufficient.'" Inherency "may **not** be established by **probabilities**

[7] Verdegaal Bros. V. Union Oil Co. of Calif., 2 U.S.P.Q 2d 1051, 1053 (Fed. Cir. 1987).
[8] See MPEP §2112.
[9] Ex Parte Levy, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990).

or possibilities." Rather, "the extrinsic evidence 'must make clear that the missing descriptive matter **is necessarily present** in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.'" [10]

As detailed above, the Yao et al. reference specifically discloses antisense p11 polynucleotides that affect the amount of "**cellular p11 protein**." In contrast, amended claim 1 is directed to a **composition** which comprises an isolated antisense p11 polynucleotide and a pharmaceutically acceptable carrier that affects a change in the activity of extracellular p11. Thus, not only is the claimed composition, surface p11 and a change in the level of extracellular plasminogen activation not "necessarily present" in the Yao et al. reference, but one skilled in the art would not expect that the teaching of the Yao et al. reference (namely modulating the amount "**cellular** p11 protein") "*may* result" in a change in the level of **extracellular** plasminogen activation. In view of the Office action, the Office's determination of inherency was apparently based on the technical misconception that the compositions of the invention "change the level of plasminogen activation **in a cell**." As detailed above, however, plasminogen is found in the blood and may bind to p11 on the **surface** of a cell. Moreover, the Office has not shown that the antisense p11 polynucleotide disclosed by Yao et al. would necessarily work in an extracellular environment to modulate plasminogen levels in the blood **when** administered as a composition of an isolated p11 antisense polynucleotide and a pharmaceutically acceptable carrier, as required by claim 1.

In conclusion, the Office has not provided accurate technical reasoning to support the determination of inherency, nor has the Office cited evidence to make clear the composition of claim 1 is necessarily present in the Yao et al. reference or that the teaching of the reference may result in a change in the level of extracellular plasminogen activation. Thus, the Yao et al. reference does not anticipate claim 1. Moreover, claims 2-4, 17 and 18, which depend from claim 1, are likewise patentable over these references for the reasons stated with respect to claim 1. Claims 5-8 and 18, which recite particular sequences of isolated antisense p11 polynucleotides and

[10] In re Robertson, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted).

particular cells, respectively, are further patentable over Yao et al. because the recited sequences and cells are not disclosed in Yao et al.

(b) 35 U.S.C. §103 rejections

Claims 1-4, 17 and 18 are not rendered obvious in view of Yao et al. A prima facie case of obviousness requires a showing that the prior art reference(s) teach or suggest all claim limitations. In the present case, for all of the reasons detailed in III(a), Yao et al. does not disclose, either explicitly or inherently, all of the claim elements of claim 1-4, 17, or 18.

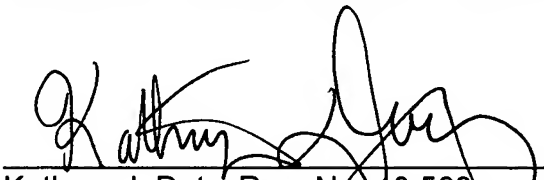
IV. Conclusion

In light of the foregoing, the applicant requests entry of the claim amendments, withdrawal of the claim rejections, and solicit an allowance of all pending claims. The Examiner is invited to contact the undersigned attorney should any issue remain unresolved.

The Commissioner is hereby authorized to charge any fees which may be required to Deposit Account No. 50-1662.

Respectfully submitted,

POLSINELLI SHALTON WELTE SUELTHAUS PC



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